to routine tuberculosis evaluation, biopsy specimens of liver and bone marrow aspiration be cultured for acid-fast organisms. A clinical trial of anti-tuberculosis agents may be indicated.

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Acute Cadmium Fume Poisoning in Welders—A Fatal and a Nonfatal Case in California

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OCCUPATIONAL EXPOSURE to cadmium is certainly as old as man's use of metals, and likely dates back more than four thousand years, into the bronze age. Even though Aristotle recorded his observations in the Fourth Century, B.C., and though acute pulmonary illness and death from exposure to cadmium oxide fumes have been described repeatedly in the medical literature, it is still a diagnosis that is overlooked. To the welder, cadmium presents an often unsuspected and probably a greater hazard than any other metal. Freshly generated cadmium oxide fumes are so toxic that they are reported to have been considered for use in chemical warfare.[8]

Reports of Cases

CASE 1. After less than two hours' brazing* with a cadmium-silver alloy, a 35-year-old white male welder complained of feeling ill. He had been brazing indoors, without any supplementary dispersing or exhausting ventilation or respiratory protective device. Although malaise continued, he finished his shift and went home, after an estimated maximal brazing fume exposure time of two and a half hours of the six and a half he had worked that day. The next day he felt worse and did not go back to work. By then severe cough and chest pain had developed, with shortness of breath, increased malaise and fever. A relative noticed that the welder's face looked blue. An expert welder, the patient attributed all of these symptoms to "welder's fever," which he had had before. Finally, one day later, he was persuaded by a relative to see a physician. As the patient did not know that the silver brazing alloy contained cadmium, he could not so inform the physician, who obtained a history of possible welding fume inhalation.

On examination, the patient was observed to be coughing considerably, but no cyanosis was noted. The pulse rate was 100 and blood pressure 125/80 mm of mercury. The temperature was not recorded. The breath sounds were harsh, but no adventitious sounds were noted. A diagnosis of chemical bronchitis was made. A tetracycline antibiotic was prescribed, together with an antitussive with codeine, plus the use of a vaporizer and increased intake of fluids. The patient was advised to return one or two times within the next five to seven days or as he felt necessary. Back at home, the welder felt improved during the next day. However, the following day he was found dead in his bedroom early in the morning.

The total time between exposure to the cad-

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*Silver brazing is commonly and mistakenly called "silver soldering" even by welders. Brazing is the process of soldering with a relatively hard to fuse alloy, at temperatures higher than those needed with fusible solders.

TABLE 1.—*Concentrations of Metals (Wet Basis) Noted on Tests of Necropsy Specimens in Case 1, with Normal Values Shown in Parentheses*

Source	*Cadmium*	*Antimony*	*Arsenic*	*Copper*	*Zinc*
Lung (μg/gm).....	4.1 (<0.5-1.3[1])	N.D.	N.D.	3 (0.9 - 2.34[1])	3 (8.6 - 23.4[1])
Liver (μg/gm).....	5.0 (0.6-5.78[1])	N.D.	N.D.	35 (3.2 -22.1[1])	35 (22.0 -100.3[1])
Blood* (μg/gm)..	N.D. (0.0[2])	N.D. (0.0[2])	N.D. (0.02[2])	15 (0.72- 1.25[4])	15 (4.9 - 12.7[4])
Urine* (μg/ml)...	0.5 (0.0[3])	N.D. (0.0[3])	N.D. (0.1[3])	10	10 (0.14- 0.93[5])

The tests were performed by Air and Industrial Hygiene Laboratories of the State Department of Public Health, Berkeley.
N.D.=Not Detected
*Cotter, et al.,[3] cite Cadmium levels in poisoning cases for *blood* ranging from 1.2 to 3.8 μg/gm, and for *urine* ranging from 0.1 to 0.36 μg/ml.
Harmful Exposure Level (urine)[6]=0.1 mg Cadmium/Liter, or 0.1 μg Cadmium/ml.
NOTE: For references, see list at end of article.

mium oxide fumes and death was just under four days. At autopsy, performed the day of death, an abundance of dark fluid was noted in the nares. Among other findings was massive pulmonary edema with extreme pulmonary hemorrhagic congestion. Microscopically, lung tissue showed edema, bronchial de-epithelialization, with infiltration of large cells in the small bronchi and the alveolar septa. Results of polarographic and emission spectrographic analysis of tissues and body fluids for five different elements are shown in Table 1. The composition of the silver brazing alloy used by the patient was as follows: Cadmium, 26 per cent; silver, 47 per cent; zinc, 15 per cent; copper, 12 per cent.

The final diagnoses were: Acute cadmium oxide fume poisoning, cadmium pneumonitis and pulmonary edema due to cadmium.

CASE 2. A 28-year-old white male welder in the same company as the patient in Case 1 was also exposed to the same brazing fumes, but to a lesser degree. Exposure occurred a few days after the first welder's death had become known, and the cause of it suspected. By then certain precautions had been taken: The process had been transferred outdoors, and stationary exhaust ventilation had been provided at the source of the fumes. At the end of three days of silver brazing—after an estimated maximal brazing fume exposure time of nine and two-thirds hours—the patient felt ill and sought medical attention. Seen early that evening at the emergency room of one of the local hospitals, he said that he had been brazing with a cadmium-containing alloy and had begun to have stomach cramps at about 6 p.m. At that time, blood pressure was recorded at 96/50 mm of mercury and oral temperature at 37.1°C (98.8°F). He was admitted to hospital immediately. On closer questioning, the welder gave a history of cough, shortness of breath, generalized malaise, nausea, diarrhea and abdominal cramps, all of sudden onset.

On physical examination the patient was alert and cooperative and apparently in no distress. No cyanosis was noted. Blood pressure was 122/66

TABLE 2.—*Results of Tests Done During Hospital Admission* (Case 2)*

Chemical		*Blood Morphology and Serology*		*Urinalysis*	
Serum:		Erythrocytes	5.3×10^6/cu mm	Specific gravity	1.016
Protein	6.2 gm/100 ml	Hemoglobin	13.4 gm/100 ml	pH	5
Albumin	3.9 gm/100 ml	Leukocytes	13,600/cu mm	Albumin	0
Globulin	2.3 gm/100 ml	Polys.	66 per cent	Sugar	0
A/G	1.7	(Segm.	55 per cent)	Microscopic:	
SGOT	124 units	(Nonsegm.	11 per cent)	Erythrocytes	0
Bilirubin		Eosinos.	7 per cent	Leukocytes	many
Direct	0.2 mg/100 ml	Lymphos.	25 per cent	Epith.	+
Total	0.9 mg/100 ml	Not Stated	2 per cent	Casts	0
		Total	100 per cent	Bacteria	0
Blood:				Crystals	0
Cadmium†	<2 μg/100 ml	Hematocrit	46.5 per cent		
		Sedimentation rate	4 mm/hr (corrected)		
Urine:					
Cadmium†	<1 μg/100 ml	Venereal Disease Research Laboratory	Nonreactive		

*Specimens collected and reported during first day of admission.
†Collected during first day of hospitalization, and reported 11 days later—nine days after the patient's discharge.

TABLE 3.—*Results of Analysis* of Biological Specimens (Case 2)*

Specimen	*Cadmium Concentration*
Blood	0.08 mg Cd/100 ml
Urine	0.05 mg Cd/Liter

The normal value for Cadmium in blood and urine is none.[3,6,7]
Harmful Exposure Limit (urine)[6]=0.1 mg Cadmium/Liter, or 0.1 μg Cadmium/ml.
*Performed by AIH Labs., Berkeley; collected 13 days after exposure, and 10 days after discharge from hospital.

mm of mercury. The only abnormal physical findings were wheezing at the bases of the lungs and mild epigastric tenderness. A diagnosis of cadmium poisoning was made, and, in anticipation of pulmonary edema, positive pressure oxygen therapy was started immediately. General supportive therapy also was carried out. Chest roentgenograms taken the next day showed no abnormality. Data from tests done on the day after admission are shown in Table 2. Blood and urine specimens were sent to an outside laboratory for determination of cadmium content. Eleven days later a report was received showing less than 2 μg of cadmium per 100 ml of blood and less than 1 μg per 100 ml of urine (Table 2).

No clinical or other evidence of pulmonary involvement was noted in the next two days. On the positive pressure oxygen therapy the patient improved dramatically, and he was discharged less than 72 hours after admission and returned to work within ten days of that date. He did not work with any cadmium-containing product and at last report was well. Through the county's Health Department, blood and urine samples were collected 10 days after the patient was discharged from hospital—13 days after his last exposure to cadmium oxide fumes. These specimens were analyzed by the Air and Industrial Hygiene (AIH) Laboratories of the State Department of Public Health for cadmium concentrations, and the results are shown in Table 3.

The discharge diagnosis made was: Acute cadmium oxide fume poisoning.

Work Environment Study

Shortly after the cause of the disease in Cases 1 and 2 was suspected, an industrial hygiene evaluation of the exposures to cadmium oxide fumes during the brazing operations in question was done. It was judged unfeasible and too dangerous to duplicate and evaluate the indoor work operation, for the risk of contaminating the work environment was too great.

Consequently, a study was done only of the outdoor work operation closely simulating the work exposure involved in Case 2. The findings are reported in Table 4.

The maximum acceptable concentration for cadmium oxide fume has been established by the State Division of Industrial Safety to be 0.1 mg per cubic meter of air (mg/M³). By definition, the maximum acceptable represents "the concentration of fume in which it is considered safe for men to work, whether for brief periods or for full working periods daily for an indefinite time."

Acute cadmium poisoning can occur in two ways, by inhalation of freshly generated cadmium fumes, and by ingestion of cadmium compounds.

Inhalation. In cases of inhalation poisoning, almost invariably the patient is an industrial worker, a high proportion of them welders. The intoxication results from the inhalation of high concentrations of cadmium fumes, typically following heating, welding or burning of cadmium-

TABLE 4.—*Atmospheric Concentrations of Cadmium Oxide Fumes§ Mock-up of Work Operation of Case 2*

Location	*Operation*	*Atmospheric Conc. mg/M³**	*Remarks*
1. Vertical tube stand, outdoors	Brazing with silver-cadmium alloy	0.14	OBZ† sample, with suction hose approximately one foot from alloy operation.
2. Same as (1)	Same as (1)	0.02	OBZ sample, suction hose approximately 8″ from alloy operation.
3. Same as (1)	Same as (1)	0.01	OBZ sample, suction hose approximately 6″ from alloy operation.
MAC‡		0.10	

*mg/M³=milligram of cadmium oxide per cubic meter of air.
†OBZ=operator's breathing zone.
‡MAC=maximum acceptable concentration as stated in the General Industry Safety Orders of the California State Division of Industrial Safety.
§Collected by the Bureau of Occupational Health, and analyzed by the Branch Public Health Laboratory California State Department of Public Health, Los Angeles.

containing metals or brazing with silver-cadmium alloys.

Symptoms are those of bronchial and pulmonary irritation. Usually they first appear several hours after exposure, but sometimes they appear immediately, and consist of dryness of the throat, cough, headache, dizziness, fever, chest pain and breathlessness. After 12 to 36 hours the chest pain and the dyspnea become extremely severe and intense cyanosis may develop. Delayed pulmonary edema may develop as late as 12 hours after exposure, and delayed hemorrhagic interstitial pneumonitis may develop as early as four days after exposure.[2,10] Moreover, there may be gastrointestinal symptoms and signs such as those associated with cadmium poisoning from ingestion. If exposure to cadmium fumes is sufficiently severe, death occurs in from four to nine days. Patients who survive usually recover without permanent damage,[2,5,9,10,16] with decreasing intensity of the respiratory distress in eight to 14 days.[13]

Ingestion. The acute symptoms of cadmium poisoning by ingestion are those of severe gastroenteritis. They resemble those of food poisoning—nausea, abdominal distress, severe vomiting, diarrhea and weakness, lasting about 24 hours and followed by complete recovery. However, collapse due to gastroenteritis and dehydration may occur in unusually severe cases. Several outbreaks of "food poisoning" have been traced to contamination of food and drink by cadmium salts released from cadmium-plated food containers or utensils. As such containers are no longer in general use in this country, such cases are now rare.

Differential Diagnosis

Since, as was mentioned earlier, acute cadmium oxide fume intoxication is almost invariably due to an occupational (industrial) exposure, it is imperative to ask for and obtain as precise a work history as possible. Moreover, since the presenting symptoms may be "mixed"—referable to the respiratory and gastrointestinal systems—even after the inhalation of such fumes only, the differential diagnosis will have to include:

Metal fume fever*; polymer fume fever; other occupational causes of acute pneumonitis and/or pulmonary edema**; non-occupational causes of acute pneumonitis and/or pulmonary edema; acute gastroenteritis—viral, bacillary, bacterial toxin; acute gastroenteritis due to ingestion of poisonous animals and plants; and other causes of acute gastroenteritis.

Attention must be drawn to the similarities between the symptoms of early acute cadmium fume inhalation poisoning and metal fume fever ("welder's fever"). The latter is a benign, self-limiting condition, characterized by chills, dry cough, dry throat, fever, nausea, vomiting, headache, fatigue, weakness and chest discomfort. It occurs frequently in welders and in other metal tradesmen a few hours after exposure to and inhalation of fumes of various metals, most commonly zinc.[16] The symptoms usually disappear within a day. The worker who has been unknowingly overly exposed to cadmium fumes may mistake his condition for metal fume fever and not seek medical attention. Moreover, even if after a delay a physician is consulted, the similarities between the two diseases, plus unawareness by the worker and the physician that cadmium was involved, may lead to a wrong diagnosis and the wrong treatment for a condition that is a medical emergency. As a rule of thumb, given the right work history, if the symptoms have lasted for over 24 hours and the chest pain is severe, cadmium fume poisoning should be suspected.

Diagnostic Procedures and Tests

Physical examination of the chest is of little assistance in early diagnosis or prognosis. Chest roentgenographs may show scattered patchy infiltration of the lungs, but these may not appear for up to three or four days after over-exposure. Biochemical tests indicative of tissue destruction or organ dysfunction—serum glutamic oxaloacetic transaminase (SGOT), bilirubin and the like—plus other routine blood and urine tests, are indicated, although they may not contribute much to early diagnosis or prognosis. A good work history plus a high index of clinical suspicion is required, therefore, to identify illness from cadmium fumes.

Fortunately, in a diagnostic sense, cadmium, once incorporated in the body, is retained for long periods. Traces of cadmium have been detected as long as 15 weeks after exposure. It is excreted slowly, via the bile, in the feces.[15] Significant concentrations can be detected in urine and blood at least as long as two weeks after overexposure (Table 3) if sensitive analytical tech-

*Also called "welder's fever," "galvanized fever," "foundryman's fever," which may be caused by the fumes of lead, copper, magnesium, mercury, zinc, tellurium and a few others.[16]

**Beryllium, bromine, chlorine, hydrazine, nickel carbonyl, nitrogen oxides, phosgene, phosphine, selenium, zinc stearate, dimethyl sulfate, hydrogen fluoride, ozone.[11,16]

niques are used—for example, hypopolarography and emission spectrography, but these are elaborate procedures, and results may take a week or longer to be reported.

Treatment

Acute poisoning by inhalation of freshly generated cadmium fumes is a medical emergency. Therapy consists of:[4,11,16]

- *Oxygen* with inspiratory phase positive pressure.
- *Strict limitation of activity,* due to the "lag phase" of pulmonary edema, even if no symptoms are immediately apparent, until a reasonable period has passed.
- *Broad spectrum antibiotics*—the tetracyclines or semi-synthetic penicillins—with any sign of pulmonary infection.
- *Nebulized bronchial dilators* for bronchospasm—for example, isoproterenol (Isuprel), epinephrine.
- *Cortisone* intravenously for several days, followed by steroids by mouth in more severe cases.
- *Nebulized non-irritant bronchial detergents* to increase mucus excretion.
- *Analgesics* for chest pain. Contraindicated because of pulmonary edema are morphine and opiates and respiratory depressant drugs. Digitalis is also contraindicated, since pulmonary edema of this type is not of cardiac origin.
- *Calcium ethylenediamine tetraacetic acid* (EDTA, Edathamil), a chelating agent, in a dose of 0.5 gram orally every two hours, while awake, for one to two weeks. (This drug is effective, but may produce renal damage; hence, frequent urine and renal function monitoring is necessary.) Due to the nephrotoxicity of the products excreted, Dimercaprol® (BAL, British Anti-Lewisite) is contraindicated here.[13,16]

The importance of holding the patient's activity to a minimum cannot be emphasized enough. Neglect of this injunction has accounted for increased morbidity in many instances. An essential part of the therapy is to prevent the patient from returning to work until the occupational health hazard has been corrected.[11]

Discussion

The industrial hygiene study of the work situation closely duplicating that of Case 2 indicated that under some conditions the maximum allowable concentration (MAC) of 0.1 mg per cubic meter of air for cadmium fumes could be exceeded, and that, therefore, the outdoor work operation could be hazardous to the health and life of any welder doing such brazing (Table 4). From the same study, it can be inferred that, if the operations were conducted inside the building—as they were by the welder in Case 1—with no exhaust ventilation, atmospheric concentrations of cadmium oxide would have exceeded, by at least one order of magnitude, the levels actually measured—that is, they would have been at least ten times the MAC, or at least 1 mg per cm of atmosphere.

In Case 1 a review of the work history and exposure; the onset of symptoms and signs and the clinical history and findings typical of acute cadmium fume poisoning; the pathological findings, both gross and microscopic; and the AIH Laboratory findings of grossly elevated cadmium concentrations in the lungs, as well as in the urine, where the harmful exposure limit was exceeded by five times (Table 1)—all corroborated the diagnoses derived initially from the autopsy and the occupational exposure.

In Case 2 the clinical diagnostic and therapeutic problems were much different. The initial symptoms—given the fact that the cause was suspected from the start by both the welder and the physicians—were essentially those of acute gastroenteritis, with few symptoms referable to the respiratory system. Only a few wheezes were heard at the base of the lungs, and on only one occasion. It is a possibility that the immediate use of oxygen therapy by positive pressure helped rid the lungs of loose cadmium oxide particles which, had they reacted further with the alveolar tissues, might have produced the typical pulmonary complications. From the industrial hygiene study, and from the occupational history, it is known that this patient was most likely exposed to a hazardous concentration of cadmium oxide fumes. It is possible that besides inhaling he also swallowed these fumes, and that the symptoms and clinical findings were due mostly to the ingestion of cadmium oxide particles. Cadmium, however, is not absorbed from the gastrointestinal tract.[2] The fact that in this case the blood and urine showed cadmium 13 days after the last exposure to the brazing fumes, and that gastrointestinal symptoms and signs can be produced by the inhalation of fumes,[2] corroborate the diagnosis of acute cadmium oxide fume inhala-

tion poisoning. This series of events also raises the interesting and therapeutically worthwhile hypothesis that in such cases the judicious and immediate application of oxygen therapy by positive pressure may not only lessen the severity but also shorten the duration of the illness. The elevated serum SGOT and bilirubin (Table 2) point to an acute intracellular liver dysfunction or to massive tissue destruction. Both are known to be produced in the inhalation type of poisoning.[2] The elevated leukocyte count shown in Table 2 indicates an acute inflammatory process also.

In Case 1, the higher than normal concentrations of copper in tissues and fluids, and of zinc in blood and urine (Table 1), cannot be disregarded. No harmful exposure levels for these two metals in blood and urine appear to have been determined.[6] MAC's exist for the fumes of these two metals, but the industrial hygiene study did not test the work atmosphere for them. No conclusions, therefore, can be made as to the significance of their concentrations in the tissues and body fluids of the patient, other than that they were higher than usual as reported. Silver fumes are not known to present a health hazard. Copper and zinc, however, are known causes of metal fume fever.[16] It is known that the presence of mixtures of substances of similar chemical and toxicological properties makes their effects additive in calculating an MAC.[6]

In both Case 1 and Case 2, it can be postulated, therefore, that the effects of the cadmium, copper and zinc fumes were at least additive, and possibly synergistic.

Review and Comments

Deaths from acute cadmium poisoning are extremely rare. In the United States there have been fewer than 20 reported officially in the last 50 years, and only three reported in the medical literature since 1956.[5] Another fact is that every one of these deaths has occurred in industrial workers, especially in welders, and was due to the inhalation of freshly generated cadmium fumes. This hazard is not confined to the spraying, brazing or overheating of alloys or metals containing cadmium. It can also arise from the welding, burning or heating of cadmium-plated steel and other metals.

Domestic industrial cadmium production and shipment increased during 1965.[14] Moreover, it appears that cadmium-containing brazing alloys are being more widely used, not only in industry, but also in high school and university industrial arts and sculpture courses, as well as by hobbyists who make their own jewelry, or repair their own guns and pistols. Since the time that the study of these two cases was reported (January 1966), official reports of another three deaths, and preliminary reports of approximately six other cases, all from acute cadmium oxide fume poisoning, have been received from other states.[8] Another nonfatal case of acute pulmonary edema in a welder brazing with a similar alloy was reported recently from Ontario, Canada.[12]

Summary

Two cases of acute cadmium oxide fume inhalation poisonings—one fatal and the other nonfatal—which occurred recently in California welders are presented. This report also presents (1) a summary of an industrial hygiene evaluation of the work situation atmospheric concentrations of, and exposure to, cadmium oxide fumes of these two welders; and (2) an occupational medical evaluation of the relationship of such exposures to the death and illness of the same workers. Treatment, a short review of the medical and toxicological literature are discussed. As well, mention is made of another 10 cases of the same etiology—including three fatal ones—which have been officially or tentatively reported from other states and Canada since these two California cases were studied and reported.

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